#175-A

TOBACCO INDUSTRY RESEARCH COMMITTEE
150 EAST FORTY SECOND STREET NEW YORK 17, N.Y.

Application For Research Grant

Date: August 9, 1957
(Resubmitted 4/24/58)

1. Name of Investigator: F. William Sunderman, M. D., Ph.D.

2. Title: Director of the Division of Metabolic Research
Clinical Professor of Medicine

3. Institution & Address: Jefferson Medical College
1025 Walnut Street
Philadelphia 7, Pa.

4. Project or Subject: Metabolism of Trace Metals: Role of Metallic Carbonyls in Pulmonary Carcinogenesis

5. Detailed Plan of Procedure (Use reverse side if additional space is needed):

The proposed investigations will be directed toward studying the effects produced by long-continued exposure of experimental animals to repeated sublethal inhalations of metallic vapors. Attention will be focused on the carcinogenicity and the intermediary metabolism of these materials. The chronic effects from inhalation of metallic vapors will be investigated as they may pertain to the inhalation of tobacco smoke.

Background Information

For the past several years our laboratory has been interested in the toxicity of various metallic carbonyls used by industry. (Reprints are attached.)

Metallic carbonyls are formed from the reaction of carbon monoxide with metallic ions, including nickel, coblat, iron, etc. Nickel carbonyl, $Ni(CO)_4$, for example, is one of the most toxic compounds encountered industrially. Its high volatility makes it difficult to avoid exposure by inhalation during handling. To avoid effects of acute poisoning, the maximal allowable concentration has been set at 0.04 parts per million in air.

Over the past score of years a number of reports have appeared in the literature attributing carcinogenic properties to the inhalation of metallic carbonyls, especially nickel carbonyl. Most of the evidence has

been obtained from studies on workers in the nickel industry who developed cancer of the respiratory passages after exposure to vapors of nickel carbonyl over a period of ten or more years. The carcinogenic property of nickel carbonyl was first observed by Baader in 1924 and the first report that an excessive number of cases of carcinoma of the lungs and nasal passages developed among nickel workers was made by Grenfell in 1932. An analysis of death certificates issued in South Wales between 1907 and 1934 indicated that 34% of the cases of cancer of the respiratory organs occurred in nickel workers. Barnett noted that, from 1923 to 1948 inclusive, 49 cases of cancer of the nose with 46 fatalities and 82 cases of cancer of the lungs with 72 fatalities were reported from nickel workers in England.

Our laboratory has studied the effects of acute and chronic exposures of nickel carbonyl in rats. Although rats are highly resistant to pulmonary carcinoma, nevertheless, squamous metaplasia of the bronchial epithelium has recently been encountered in surviving animals following chronic exposure to nickel carbonyl. Our evidence thus far is suggestive (although inconclusive) that chronic exposure to nickel carbonyl may produce cancer of the respiratory passages in the rat. It is our desire to extend these studies and to correlate them with the effects of inhalation of tabacco smoke.

6. Budget Plan:

Proposed Budget for First Year

Salaries	$10,800
Expendable Supplies	1,500
Permanent Equipment	3,250
Overhead	1,875
Other (Travel etc.)	250
Total	$17,675

7. Anticipated Duration of Work: **Four years**

8. Facilities and Staff Available:

Our laboratory is staffed with experienced investigators and technicians and is well equipped for metabolic studies. In addition, our division maintains a toxicity laboratory with special animal quarters. The toxicity laboratory is equipped with a constant flow chamber for exposure of experimental animals to gases and volatile liquids (see reprint for description of chamber.

9. Additional Requirements:

Staff - A competent physician-investigator will be available in September for work on this project.

Equipment - A spectrophotometer with fluorimeter attachment will be needed. Eventually there will be need for a spectrograph.

10. Additional Information (Including relation of work to other projects and other sources of supply):

This work would extend, compliment and correlate with studies on the toxicity of nickel carbonyl that are being undertaken for the Atomic Energy Commission.

/s./ George A. Bennett, M. D. Dean

Signature /s./ F. William Sunderman
Director of Project

/s./ George M. Ritchie
Business Officer of the Institution

George M. Ritchie, Controller

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Salaries	$10,800	
Expendable Supplies	1,500	
Permanent Equipment	3,850	
Overhead	4,275	
Other (Travel etc.)	1,250	
Total	$21,675	

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RESEARCH & DEVELOPMENT DEPT.

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Signature /s/ F. William Sunderman
Director of Project

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